Journal of Medical and Health Studies
ISSN: 2710-1452
DOI: 10.32996/jmhs
Journal Homepage: www.al-kindipublisher.com/index.php/jmhs

JMHS
AL-KINDI CENTER FOR RESEARCH AND DEVELOPMENT

| RESEARCH ARTICLE

Paraneoplastic Syndrome Associated Immune Complications: A Narrative Review of the Literature

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| ABSTRACT

Paraneoplastic syndromes occur in cancer patients due to an alteration in their immune response. There are several factors that may result in the occurrence of paraneoplastic syndrome, including the presence of abnormal cytokines that cause widespread effects throughout the body. The paraneoplastic syndrome may be present in patients before a diagnosis of cancer, and thus, understanding it is crucial as it will help achieve a timely diagnosis, which may aid in improving the chance of treatment. It is associated with several complications/presentations in patients. In this review, we will discuss several paraneoplastic syndrome associated complications, including hypercoagulable state, venous thromboembolism, arterial thromboembolism, thrombotic microangiopathy, disseminated intravascular coagulation, and malignancy associated non-bacterial thrombotic endocarditis. Although some are rare, it is vital for clinicians to have a knowledge of each to allow time for management.

| KEYWORDS

Paraneoplastic Syndro; Immune Complication; abnormal cytokines

| ARTICLE INFORMATION

ACCEPTED: 12 December 2023 **PUBLISHED:** 04 January 2024 **DOI:** 10.32996/jmhs.2024.5.1.2

1. Introduction

Paraneoplastic syndromes (PNS) are the result of an altered immune response due to either the production of specific antibodies, abnormal release, or the release of abnormal cytokines [Muller et al. 2018]. They are characterized by widespread effects that occur alongside specific types of cancers without being directly caused by the local spread or metastasis of the tumor. These syndromes cannot be explained by factors such as nutrition, metabolism, infections, or medical interventions [Bussat 2018]. In certain cases, PNS may become evident before the diagnosis of cancer. Consequently, identifying these syndromes in a timely manner could potentially lead to the detection of an otherwise hidden tumor at an early stage when it is more easily treatable [Pelosof 2010]. The criteria for diagnosing a PNS include the existence of cancer, clinical symptoms that are not directly caused by a primary tumor

or its metastases, exclusion of other non-cancerous causes for the symptoms, a simultaneous progression or development of the PNS alongside cancer cytokines [Muller et al. 2018].

Our comprehension of PNS has progressed, and we now recognize a diverse range of syndromes affecting multiple systems, including endocrine, hematologic, rheumatologic, and ophthalmological systems, as well as the skin. Conditions like glomerulopathy and coagulopathy may also occur. These syndromes can manifest in different types of cancer [Sebastian et al. 2019]. Endocrine irregularities observed in PNS can be attributed to the capacity of cancerous cells to generate and release biologically active hormones and peptides [Onyema et al., 2022]. Paraneoplastic neurologic syndromes occur when there is an immune response that mistakenly targets both tumor cells and components of the nervous system, leading to neurological manifestations [Pelosof 2010]. The range of neurological symptoms associated with PNS is broader than what has traditionally been acknowledged, and these symptoms can be mistakenly diagnosed as neurodegenerative disorders or cancer progression [Zekeridou et al. 2019].

PNS can have significant hematologic consequences. Thrombosis is a prevalent complication associated with cancer and ranks as the second major cause of death among cancer patients. Various factors related to the immune response against neoplasms, including the production of acute phase reactants, abnormal protein metabolism, necrosis, and changes in blood flow dynamics, collectively increase the activation of blood coagulation in individuals with cancer [Caine et al. 2002]. Additionally, patients with cancer have an elevated risk of bleeding, which can be further complicated by using anti-thrombotic treatments [Sabatino et al. 2020]. Lung cancer, particularly the small cell histological variant and adenocarcinoma, is the primary culprit behind the occurrence of PNS. These syndromes are not directly linked to the primary tumor or its metastases. Instead, they arise from intricate immune-inflammatory, degenerative, and vascular alterations that take place in distant parts of the body [Dumansky et al. 2018]. The discovery of antibodies in the blood of patients with different tumor types revitalized the investigation of PNS [Giometto et al. 1999].

In recent years, numerous proteins secreted by tumors have been identified. PNS can often serve as an initial indication of an underlying malignancy, potentially enabling early detection of cancer. However, the presence of PNS does not necessarily predict the outcome of treatment for the underlying cancer. Consequently, proteins secreted in PNS can be explored as tumor markers for diagnostic purposes [Bilynsky et al. 2015]. With the continuous advancements in therapies for various types of tumors and the widespread utilization of highly targeted diagnostic methods, patients with neoplasms are expected to experience extended lifespans. Consequently, it is likely that the prevalence of PNS will also rise [Dimitriadis et al. 2017].

2. Hypercoagulable state in Paraneoplastic Syndrome

A hypercoagulable state is defined as a condition in which there is an increased tendency for blood clot formation to occur, a phenomenon known as thrombosis. It is possible to classify hypercoagulability in cancer patients as Type I or Type II. Heparinase secreted by tumors increases the degradation of endogenous heparin, resulting in type I thrombocytopenia. Those who suffer from type II hypercoagulability have several factors involved, including the patient, the tumor, and/or their treatment [Nasser et al. 2020]. The hypercoagulable state seen in cancer patients is a result of several contributing factors, including the release of tissue factor (TF), a procoagulant that is secreted by malignant tissue, as well as the interchange among leukocytes, endothelial cells, and platelets. This interaction promotes inflammation and worsens the hypercoagulable condition in these individuals. Overall, these various factors collectively drive the development of the hypercoagulable state in cancer patients [Zekeridou et al. 2019]. Coagulation abnormalities, platelet and adhesion activations, and endothelial cell dysfunction are also seen to contribute significantly to hypercoagulable states in cancer related patients.

Cancer is commonly associated with a pro-hemostatic condition. As a result, patients with malignancies tend to be predisposed to a condition known as venous thromboembolism (VTE), which can occur before a cancer diagnosis is established. Not only can VTE result, but cancer can also lead to the complication of coagulation systemically that can cause disseminated intravascular coagulation (DIC), thrombotic microangiopathy or even a combination of these disorders [Sebastian et al. 2019]. As far as the evidence is seen in this hypercoagulable state, cancer patients tend to present with abnormalities in their lab coagulation tests, indicating a hypercoagulable state taking place. For example, tumor-specific proteins were detected in an ovarian cancer patient's plasma exosome, especially in epithelial ovarian carcinoma (EOC). EOC patients have impairments in their coagulation functions. Studies have been conducted to examine the role of exosomes in coagulation, including screening of several genes involved in the coagulation cascade, which evidence indicating their use as a promising propitious factor that can be used in diagnosis and prognosis in both disease progression and metastasis [Zhang et al. 2019]. Consequently, the management of "cancer-related thrombosis" (CAT) must be handled differently from thrombosis seen in non-cancer patients, as there are differences in the mechanism of thrombi formation in cancer versus non-cancer patients [Onyema et al. 2022].

Thrombotic events in individuals with cancer are classified as CAT, necessitating tailored and specialized treatment strategies. Fibrinolytic proteins, inflammatory cytokines, procoagulant proteins and microparticles are all produced from cancer cells, which demonstrates evidence of a hypercoagulable process occurring in cancer patients. Additionally, the formulation of adhesion

molecules on cancer cells fosters binding to vascular cell receptors, thus promoting prothrombic properties [Onyema et al. 2022; Zekeridou et al. 2019; Caine et al. 2002]. The production of TF from cancerous cells is often highlighted as the point of coagulation reaction initiation triggering CAT. TF leads to the activation of Factor VII, thus potentiating the formation of a complex between these two factors.

The TF complex triggers factor X activation, resulting in the generation of factor Xa. Under certain circumstances, some cancer cells can promote the production of a cancer procoagulant (CP), which acts directly on factor Xa. The activation of factor Xa potentiates increased thrombin production, further potentiating the amplification of the coagulation cascade. This amplification results in platelet activation, ultimately culminating in the development of multiple thrombi. This disturbance in the coagulation cascade, as well as damage mediated by the cytokines secreted from the cancer cells, results in the formation of venous and arterial thromboemboli [Zekeridou et al. 2019]. Cancer cells also secrete plasminogen activator inhibitor (PAI-1), which plays a role in inhibiting the fibrinolytic system. This, in turn, promotes fibrin deposition, resulting in a fibrin thrombi formation. The combination of activated platelets, fibrin, thrombin, coagulation and fibrinolysis abnormalities can lead to the development of DIC.

2.1 Venous Thromboembolism

Despite advancements in medical care, individuals with active cancer still face a remarkable risk of thromboembolic events, encompassing both venous thromboembolism (VTE) and arterial thromboembolism (ATE). Venous thromboembolism (VTE) is the most predominant type of thrombotic event seen in cancer patients. The incidence of VTE is 4 to 7 times higher in patients diagnosed with cancer compared to cancer free individuals [Gervaso et al 2021]. VTE rates in cancer patients have risen due to factors including immobility, surgical procedures, improved patient survival, higher thrombotic-risk cancer treatments, widespread use of central catheters, and increased awareness of CAT [Lobo et al. 2017]. Around 15% of cancer patients are likely to develop VTE, and interestingly, 20% of unprovoked VTE cases may be the first sign of an underlying malignancy [Gervaso et al 2021]. VTE can present in patients in the form of deep vein thrombosis (DVT) and pulmonary embolism (PE), and their risk fluctuates throughout the disease course. It reaches its highest point within the first six months following cancer diagnosis and subsequently decreases [Abdol et al. 2018, Grilz et al. 2018]

VTE is not limited to DVT and PE but can also occur in unusual locations such as the upper extremities, cerebral veins, splenic vein, splanchnic vein, portal vein and other abdominal veins. Active cancer and the use of central venous catheters are often linked to upper extremity thrombosis. Gastrointestinal malignancies are commonly associated with splanchnic or visceral vein thrombosis (VVT), ranging from 9% to 20% in different studies [Gervaso et al 2021, Pfrepper 2020]. Pancreatic and gastric cancers are classified as high-risk tumors for VTE development compared to other tumors like breast, colon-rectal, and head-and-neck cancers which are low-risk [Pfrepper 2020, Frere 2021]. Other cancers such as esophageal, ovarian, lung, non-Hodgkin lymphomas, and multiple myeloma also confer a significant risk. VTE risk is higher in cases with regional or metastatic spread compared to localized disease [Gervaso et al 2021]. Lung cancer patients have a 20-fold increased risk of VTE compared to the general population. Non-small cell lung cancer (NSCLC) carries a higher risk of VTE than small cell lung cancer (SCLC), and adenocarcinomas are also associated with a higher VTE risk when compared to squamous cell carcinoma [Anwar et al. 2019, Zheng et al. 2021]. The rate of VTE in patients with pancreatic cancer varies, with prospective studies indicating a range of 10% within 3 months after starting chemotherapy and retrospective cohort studies reporting a range of 20-40% [Pfrepper 2020, Frere 2021, Anwar et al. 2019].

Thromboembolism is a significant cause of mortality in cancer patients, ranking second only to cancer itself [Gervaso 2021]. VTE has a notable impact on both patient morbidity and mortality, with fatal pulmonary embolism occurring three times more in cancer patients compared to healthy patients [Abdol et al. 2018]. Cancer patients who experience VTE at either the time of diagnosis or within the first year tend to have a poorer prognosis. VTE diagnosis in cancer patients not only affects their quality of life but also reduces overall survival rates [Abdol et al. 2018].

Table 1: Types of Venous Thromboembolism and its associations

Types of Venous Thromboembolism	Associations	Incidence
Deep Vein Thrombosis (DVT)	Pancreatic, gastric, lung cancers, non-Hodgkin lymphomas, multiple myeloma	10% to 40% (varying studies)
Pulmonary Embolism (PE)	Pancreatic, gastric, lung, non-Hodgkin lymphomas, multiple myeloma	9% to 20% (Varying studies)
Upper Extremity Thrombosis	Use of central venous catheters	N/A
Splanchnic Vein thrombosis (including splenic vein, portal vein and other abdominal veins)	Gastric cancer, esophageal cancer	N/A

N/A – Not available

Note: Incidence rates may vary based on study design, population, and follow-up duration.

2.2 Arterial Thromboembolism

Despite arterial thromboembolism (ATE) having a higher incidence and mortality rate in the general population than venous thrombotic events, there is limited research on the epidemiology of ATE in cancer patients. In a study, myocardial infarction was the predominant form of arterial thromboembolism (ATE), comprising 41.7% of cases, followed by stroke occurring in 33.3%, and peripheral arterial events occurring in 25.0% of patients [Pfrepper 2020].

Risk factors for ATE resemble those observed in the general population, including age, male gender, hypertension, and smoking [Pfrepper 2020]. Patients diagnosed with either kidney or lung cancer have an increased risk. A study conducted by Zöller et al. indicated that patients with gastrointestinal tumors affecting the stomach, small intestine, anus, liver, and pancreas had an increased risk of coronary heart disease, 2-fold within the first six months after diagnosis. Their study also indicated that non-Hodgkin lymphoma, myeloma, leukemias, and tumors affecting the endocrine system, kidneys, lungs, and nervous system had an increased risk [19]. This difference in ATE risk among different cancers may be influenced by common risk factors, including smoking or cancer treatments, e.g. platinum-based chemotherapy, vascular endothelial growth factor (VEGF) inhibitors, and vascular endothelial growth factor receptor (VEGFR) inhibitors have been linked to increased risk of ATE [Grilz 2018].

The risk of arterial thromboembolism (ATE) is increased in the year preceding a diagnosis and peaks at the time of diagnosis and within the first three months thereafter, gradually decreasing over time [Pfrepper 2020]. Elderly lung cancer patients have a significantly increased risk of developing ischemic stroke compared to matched controls, as indicated by a Medicare claims-based study. Within 1 year of cancer diagnosis, the stroke incidence among lung cancer patients was 6.9%, more than twice the rate observed in the control group (3.2%). The risk of stroke is particularly elevated in advanced cancer stages, with stage 4 cancers displaying the highest risks [Navi et al. 2018]. A study using landmark analysis showed that cancer patients without ATE within the first three months had a predicted 2-year overall survival of 62.3%. However, patients who experienced ATE during this period had a significantly lower predicted 2-year overall survival of 24.8%. The average survival time for cancer patients after ATE occurrence was only 63 days, ranging from 36 to 233 days [18]. Thus, there was a noticeable 3.2-fold increased risk of mortality associated with ATE [Pfrepper 2020]. Few studies report a 4-fold increase in mortality in cancer patients with ATE. Accurately estimating the exact risk of ATE amongst cancer patients can be challenging as the rate of ATE may be influenced by age and cardiovascular risk factors [18]. It is crucial to identify patients at high-risk in order to modify their preexisting cardiovascular risk factors and utilize efficacious antithrombotic prophylaxis [Yu et al 2019].

Table 2: Types of Arterial Thromboembolism and their associations

Types of Arterial Thromboembolism (ATE)	Associated Cancers
Myocardial Infarction	Lung, kidney, gastric, pancreatic, polycythemia, and leukemia.
Stroke	Lung, kidney, gastric, pancreatic, multiple myeloma, polycythemia, and leukemia
Peripheral Arterial Events	Lung, kidney, gastric, pancreatic, polycythemia, and leukemia

3. Thrombotic Microangiopathy

Thrombotic microangiopathy (TMA) is due to endothelial damage leading to a group of disorders-abnormal activation of coagulation such as microangiopathic hemolytic anemia (MAHA), thrombocytopenia, occlusive (micro)vascular dysfunction leading to organ damage. TMA occurs in individuals battling patients either as a manifestation of cancer-related coagulopathy or as tumor-induced TMA (Ti-TMA), representing an uncommon manifestation of Trousseau syndrome, a paraneoplastic syndrome. In addition, TMA might arise from overlapping conditions such as infections, dose dependent toxicity linked to treatment, or a result of antibody reaction of chemotherapeutic agents [Font et al. 2022].

TMA has a comparatively low prevalence compared to venous thromboembolism. Malignancy-associated TMA is considered a rare phenomenon as several case reports and series have reported this with an approximate incidence between 0.25 and 0.45 patients per million per year [Font et al. 2022] [Price et al. 2016]. A systemic review conducted on TMA among malignancies reported associations were mostly with gastric adenocarcinoma followed by other malignancies of breast, prostate, lung, urothelial and ovarian cancers [Uruga et al. 2013; Godbole et al. 2019]. An institutional retrospective study and a few case reports furthermore reported the prevalence of TMA among patients with acute Leukemia, melanoma, Hodgkin lymphoma, aggressive non-Hodgkin lymphoma (NHL) and myeloma, and chronic lymphocytic leukemia but major predominance by adenocarcinoma as stated above holds the same. Among malignancies, solid tumors had predominance towards TMA [Gainza et al. 2014, Bayer et al. 2017]. Rare presentations in association with hepatocellular carcinoma have been documented in some case studies [Morita et al. 2019]. The prognosis of malignancy-associated TMA is generally poor, with longer survival periods recorded in gastric cancer cases that had early detection of underlying pulmonary tumor thrombotic microangiopathy (PTTM) [Fujita et al. 2023].

Another complication is cancer-associated microangiopathic hemolytic anemia (MAHA), which is a rare but fatal complication of malignancies and is associated with a poor prognosis in patients with bone marrow metastases. MAHA can present as the first presentation in patients with malignant tumors and is mainly associated with gastric, breast, and lung cancers and tumors of unknown origin. Typical laboratory findings that indicate MAHA include anemia with schistocytes, thrombocytopenia, reduced haptoglobin levels, and elevated levels of serum alkaline phosphatase, amongst other findings [Shin et al. 2011].

Autoimmune thrombocytopenia (ITP) is another complication that occurs in approximately half of patients with malignancy, occurs in 25% of patients prior to cancer, and may occur after diagnosis and treatment as a sign of recurrence. The most common incidence is amongst patients with lung and breast cancer, with rare frequencies in prostate cancer, and is notably prevalent in renal cell and ovarian cancers [Krauth et al. 2012].

3.1 Malignancy associated Non-Bacterial Thrombotic Endocarditis.

Non-bacterial thrombotic endocarditis (NBTE) is another rare condition that has been associated with cancer, amongst other diseases with a hypercoagulable state [Borowski et al. 2003]. NBTE causes aseptic masses composed of fibrin and platelets; these masses are usually found on previously healthy heart valves. Vegetations in NBTE are very febrile and easily detached, resulting in extensive vegetation compared to those witnessed in infective endocarditis. Almost 50% of patients typically present with systemic emboli, most commonly cerebral emboli [Lopez et al. 1987]. NBTE is typically diagnosed during the autopsy, but rarely can a diagnosis be made during a patient's life [Norisada et al. 2011].

The precise prevalence of non-bacterial thrombotic endocarditis (NBTE) with malignancy is unknown because it is frequently clinically dormant or an arbitrary finding, with most cases discovered in the autopsy, but some cases were reported with NBTE as the initial presentation in early malignancy [Van et al. 2011, Rahouma et al. 2023, Fernandes et al. 2022]. It is a rare phenomenon, having an incidence of 0.9 to 1.6% in adult post-mortem populations among all instances of endocarditis investigated [Rahouma

et al. 2023, Fernandes et al. 2022, Itzhaki et al. 2022]. A recent meta-analysis of 121 studies revealed lung cancer as the most common association with NBTE in neoplasm, followed by ovarian, pancreatic and gastrointestinal cancers [Rahouma et al. 2023, Fernandes et al. 2022]. The most prevalent solid tumors associated with NBTE are adenocarcinoma variants [Borowski et al. 2003]. In general, death is caused by vegetation, which causes emboli, which can lead to major consequences such as end organ damage leading to stroke, myocardial infarction etc. [Borowski et al 2003, Patel et al 2020, Savarapu et al 2021]. The prognosis for malignancy-associated NBTE is poor due to its association with advanced malignancy [Patel et al. 2020], with a mortality rate of 87% noticed during their 6-month follow-up period. Presentation of NBTE secondary to advanced malignancy with widespread thromboembolism events was described in some case studies [Gray et al. 2021, Cheung et al. 2020].

3.2 Disseminated Intravascular Coagulation

Disseminated intravascular coagulation (DIC), an acquired syndrome, is distinguished by widespread activation of the coagulation cascade throughout the body. It is a life-threatening acute emergency and can present as a chronic disease. DIC mortality is mainly dependent on the etiology, the possibility of reversibility, and the extend of coagulation impairment [Gameiro et al. 2019]. It is crucial to determine the underlying cause of DIC in order to treat it.

In a clinical study, the reported incidence of disseminated intravascular coagulation (DIC) in solid tumors was 7%. Other reports have indicated a high incidence of up to 85% in cases of acute promyelocytic leukemia [Fernandes et al. 2022]. DIC is more commonly triggered by specific cancers, notably adenocarcinomas affecting the gastrointestinal tract (often of the signet ring cell type), pancreas, breast, prostate, or lung. Furthermore, DIC can occur in patients with acute promyelocytic leukemia as well as in acute monocytic leukemia [Thomas et al. 2021].

4. Conclusion

The paraneoplastic syndrome has been associated with several complications, including a hypercoagulable state, venous thromboembolism, arterial thromboembolism, thrombotic microangiopathy, disseminated intravascular coagulation, and malignancy associated non-bacterial thrombotic endocarditis of which thromboemboli are the most commonly occurring in cancer patients and others occurring less commonly. It is vital for clinicians/physicians to have knowledge of other complications, although rare as they may be the initial presentation of patients without a diagnosis of cancer. It is also crucial to understand their mechanism to help aid in their treatment.

Funding: This research received no external funding.

Conflicts of Interest: The authors declare no conflict of interest.

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